PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2008/001678	25.12.2008	26.12.2007

International Patent Classification (IPC) or both national classification and IPC
INV. B01L3/00

Applicant
SENG ENTERPRISES LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Viskanic, Martino Telephone No. +49 89 2399-4810

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2008/001678

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2008/001678

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 11-13,15,21-33, 39-59

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 11-13,15,21-33,39-59

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-10,14,16-20,34-38

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10, 35-38
	No:	Claims	1-9,14,16-20,34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10, 14, 16-20, 34-38
Industrial applicability (IA)	Yes:	Claims	1-10, 14, 16-20, 34-38
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV.

1. Lack of unity of invention (Rule 13.1 PCT)

1.1 Reference is made to the following document; the numbering will be adhered to in the rest of the procedure (references in parentheses applying to this document):

D1: WO 03/056345

D1 in fig. 1 discloses:
a device suitable for cell studies (cf. page 5, lines 10-22 "erythrocytes, white cells"), comprising:
a base layer (400);
a planar conduit defining layer (200), including a conduit cut out of the layer (101, 102, 103);
and a planar cover layer (300) which defines a capillary flow channel (100) (cf. page 8, lines 17-22) in said conduit layer (200), said conduit layer and said cover layer acting as side walls for said capillary flow channel (cf. page 8, lines 6-16 "sample introducing part 100"),
wherein said layers are formed of substantially inert materials (cf. page 14, lines 23-27) (see also Item VIII 4.1).
The subject matter of claim 1 can thus not be considered novel over D1 in the sense of Art. 33(2) PCT.

1.2 Being the subject matter of claim 1 not novel and therefore not inventive, it cannot represent a common inventive concept. This Authority considers that the application lacks unity within the meaning of Rule 13.1 PCT and that there are 7 groups of inventions covered by the claims indicated as follows:

Groups of inventions:

A) Claims 1-3, 5-10 (inasmuch as they don't refer back to claim 4), 14 (inasmuch as it doesn't refer back to claims 4, 11-13), 16-20 (inasmuch as they don't refer back to claim 4, 11-13, 15), 34: The device of claim 1 furthermore comprising a cell holding area in fluid contact with the capillary flow channel.

B) Claims 1, 11-13 (inasmuch as they don't refer back to claims 2-10), 15 (inasmuch as it refers back to claims 1, 11-13), 28, 29: The devices of claims 1 and 28 wherein the components are linked together by adhesive

C) Claims 21-27: Kit comprising a capillary flow conduit, a cell holding area and an indication for one or both of a capillary flow rate and a cell dislocation rate

D) Claims 30-33: A method for assembling a modular device suitable for cell studies.

E) Claims 4, 35-38: A device suitable for cell studies whereby at least one array of cell holders is partially covered (masked) and connected with a capillary channel.

F) Claims 39-43: Method for forming a device suitable for cell studies adhering a plurality of layers.

G) Claims 44-59: Method and criteria for the selection and use of a cell study device according to a desired fluid flow rate and/or a cell dislocation rate.

1.3 The requirements of Rule 13.1 PCT are not fulfilled for the following reasons:

Group A) (claims 1-3, 5-10, 14, 16-20, 34): The problem addressed is regarded to be the providing a capillary device suitable for cell studies having an area suitable for holding cells. The special technical feature is regarded to be the cell holding area.

Group B) (claims 1, 11-13, 15, 28, 29): The problem addressed is to prevent contamination and/or reusability providing a possibility for opening the cover layer of the device of group A and subsequently sealing the device (cf. description, page 31, lines 3-6). The special technical feature required is a removable non-adhesive interfering layer between the cover and the middle layer.

Group C) (claims 21-27): The problem addressed is to select a kit comprising a device suitable for cell studies including a capillary flow conduit and a cell holding area according to its technical specifications. The special technical feature is an indication about one or both of a capillary flow rate or a cell dislocation rate to be

included in the kit and the corresponding method of selection, as stated on page 30, lines 38-39 of the description.

Group D) (claims 30-33): The problem addressed is to define a method of assembling a device suitable for cell studies according to desired device characteristics. The special technical feature therefore is the selection of modular parts and assembling them, as stated in the description (cf. page 30, lines 23-25).

Group E) (claims 4, 35-38): The problem addressed is to mask out a larger cell holding area to define the part of the array to be active (cf. description, page 30, lines 34-35). The special technical feature is a the masking layer.

Group F) (claims 39-43): The problem addressed is regarded to be the construction of a cell study device. The special technical features are the plurality of layers and the methods for assembling them.

Group G): (claims 44-59): The problem addressed is how to select and use a device suitable for cell studies. The special technical features are determining one or both of desired flow rates and cell dislocation rate and selecting the technical features of a device accordingly.

Remark concerning groups A and B: the common part of the two groups is represented by the device of claim 1, which is not novel (see 1.1), hence not inventive. Thus the subject matter of group A and group B cannot share a common inventive concept.

Conclusion: the subject matter of the different groups of potential inventions are addressing different problems with different special technical features. Hence the requirements of Rule 13.2 PCT are not fulfilled. Consequently, the different groups of potential inventions are not so linked, as to form a single general inventive concept (Rule 13.1 PCT).
In what follows only the searched subject matter will be examined.

Re: Item V.

Besides D1, reference is further made to the following documents:

D2: WO 2006/080000 (from the same applicant)
D3: US 2002/0187074
D4: EP 0059297

2.1 The subject matter of claim 1 is not novel over D1 (Art. 33(2) PCT), see item IV 1.1.

2.2 Moreover the subject matter of claim 1 is not novel over fig. 4a-c of D2 (Art. 33(2) PCT) for the following reasons:
a cell study device (title), comprising:
- a base layer (50);
- having a planar conduit defining surface (47) (65), including a conduit cut out of the surface (47);
- and a planar cover layer (60) which defines a capillary flow channel with said conduit surface, said conduit surface and said cover layer acting as side walls for said capillary flow channel (cf. page 19, lines 24-28),
wherein said layers are formed of substantially inert materials (cf. page. 31, lines 7-12).
Although the device of fig. 4A-C of D2 comprises fused base layer and conduct defining surface, D2 (cf. page 30, line 31-page 31, line 2) also considers its device being made of different layers. Thus the subject matter of claim 1 cannot be considered novel over D2 in the sense of Art. 33(2) PCT.

2.3 Furthermore D3 in fig. 1A-B anticipates all the features of claim 1 being:
- a cell study device (cf. [0064]
- a base layer (13);
- a planar conduit defining layer (12), including a conduit cut out of the layer (15);
- a planar cover layer (11) which defines a capillary flow channel in said conduit layer, wherein said layers are formed of substantially inert materials (cf. [0055]).
The subject matter of claim 1 can thus not be considered novel over D3 in the sense of Art. 33(2) PCT.

2.4 The subject matter of claim 35 cannot be considered involving an inventive step (Art. 33(3) PCT for the following reasons:

Document D2 in fig. 23 discloses (references in parentheses applying to this document):
A cell study device (112), comprising one array of cell holders (93); a layer masking some of said cell holders (protruding parts of holder 112); and a layer defining one or both of capillary channels and walls (87) mounted on said layer (the capillary channel being formed by the vertical walls of hole (110) and by the lid (cf. fig. 4c (60) covering the device (cf. page 19, lines 24-28).
Document D2 states the hole 110 being smaller then the picowell-bearing component (cf. page 32, lines 25-31), thus the picowells are partly masked by the protruding portions of the holder (112). Additionally D2 states that the picowell array (18) being attached to the carrier (112) employing adhesives (cf. page 32, lines 11-13). The use of a double sided adhesive layer for this purpose is well known in the art and falls under the limited number of possible fixing methods that the skilled person would apply without employing any inventive skills, thus arriving at the claimed subject matter.

2.5 The argumentation made for the subject matter of claim 35 concerning Art. 33(3) PCT applies mutatis mutandis also to the subject matter of claim 4, which is not considered to be inventive either.

2.6 The combination of subject matter arising from the following dependent claims cannot be considered novel over D1, D2 and D3 in the sense of Art. 33(2) PCT, for the following reasons:
Claim 2: cf. D1 page 5, lines 10-22, whereby introducing whole blood in the device of fig. 1 results in the capillary flow channel (100) being the place where the blood cells are held and D2 (cf. fig. 4A (18)).
Claim 3: cf. D2 page 32, lines 16-17 "grid-like component".
Claim 4: cf. D2, fig. 23.
Claim 5: cf. D1 fig. 1 wherein the area where the cells are held (100) is on top of the base-layer (400) and D2 (cf. fig. 4C (18) (50)).
Claim 6: D3 in fig. 2A discloses a micro fluidic device made of 3 layers with an air hole (26) acting as a vent (cf. [0051]) in the external layer.
Claim 7: cf. D1 fig. 1 (103) and page 8, line 16 "void" and D2, fig. 14.
Claim 8: cf. D2 fig. 4C (68) and page 20, line 25 "absorbent element" and page 24, lines 29-32.
Claim 9: cf. D1 fig. 1 (100) and page 8, line 16 "sample introducing port" and D2

figs. 10-11.
Claim 14: cf. D1 fig. 1 and D2 fig. 4C.
Claim 16: cf. D2 page 30, line 31 - page 31, line 2.
Claim 17: cf. D2 page 29, lines 7-8.
Claim 18: cf. D2 page 4, lines 9-10.
Claim 19 (see also 4.1): cf. D1 page 14, lines 23-27 and D2 page 37, line 31 - page 38, line 3.
Claim 20: cf. D2 fig. 8 (60) and fig. 9 (60)
Claim 34: cf. D1 fig. 1 (100), whereby the air release aperture (102) is on top when the device is held with the side opposing the opening of (102) at a lower position then the side of the opening (102) itself and D3, fig. 2A and [0051].
The subject matter of said dependent claims cannot hence be considered novel (Art. 33(2) PCT) over D1, D2 or D3.

2.7 Packaging a device in vacuum is a well known technique in the biomedical field, as can be seen e.g. in D4 (fig. 3 and page 6, line 33 - page 7, line 5). The subject matter of claim 10 cannot therefore be considered inventive (Art. 33(3) PCT).

2.8 Dependent claims 36-38 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of Art. 33(3) PCT in respect of inventive step, the reasons being as follows:
The subject matter of claim 36 represents constructional modifications that the skilled person would apply to the device in D2 in order to rationalise its use.
The subject matter of claim 37 is disclosed in D2, fig. 23, whereby the adhesive layer used for fixing the picowell array (18) to the holder (112) must have an aperture coinciding with the diameter of hole (110).
Regarding claim 38 the claimed height arises from the optimisation of the device of D2 as a consequence of its use.

Re: Item VII.

3.1 Independent claims are not in the two-part form in accordance with Rule 6.3(b) PCT.

3.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

Re: Item VIII.

4.1 Claim 1 in its last part ("wherein .... solution.") tries to define the claimed subject matter by relation to the use of the device. This results in a lack of clarity (Art. 6 and Rule 6.3(a) PCT), as the technical features required are not unambiguously identifiable, being these subject to modifications according to the conditions of use (e.g. the temperature). It would have been more appropriate to define the materials like in the description, on page 16, lines 17-19 as "biologically inert". Similar argumentation applies also to claim 19, which is deemed to be unclear in the meaning of Art. 6 PCT.

4.2 It appears from the application that the cell holding area is essential for the functioning of the device. Only immobilised cells can be submitted to a capillary flow of e.g. a staining solution or a reagent without being washed away by the solution itself. Thus this feature should be considered essential and so included in the subject matter of independent claim 1 (Art. 6 PCT).

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003